IN THE UNITED STATES DISTRICT COURT
FOR THE SOUTHERN DISTRICT OF NEW YORK

AMARIN PHARMA, INC., DR. JONATHAN HERBST, DR. ERIC RISHE, DR. PETER GOTTESFELD, and DR. RALPH YUNG, Plaintiffs, v. UNITED STATES FOOD & DRUG ADMINISTRATION 10903 New Hampshire Avenue Silver Spring, Maryland 20993, UNITED STATES OF AMERICA Serve to: U.S. Attorney General 950 Pennsylvania Avenue NW Washington, DC 20530, STEPHEN OSTROFF, M.D., in his official capacity as Acting Commissioner of Food and Drugs 10903 New Hampshire Avenue Silver Spring, Maryland 20933, and SYLVIA MATHEWS BURWELL, in her official capacity as Secretary of the Department of Health & Human Services 200 Independence Avenue SW Washington, DC 20201, Defendants.	)	Civil Action No. 1:15-cv-03588-PAE Oral Argument Requested

MEMORANDUM OF LAW IN SUPPORT OF MOTION FOR PRELIMINARY INJUNCTION

TABLE OF CONTENTS

TABLE OF AUTHORITIES

Page(s)

Cases

Constitutional Provisions

Internet Sources

Law Reviews

Periodicals

Regulations

Statutes

Treatises

Other Authorities

INDEX OF EXHIBITS TO THE MEMORANDUM

This motion for a preliminary injunction is rooted in the First Amendment and apposite case law, including the seminal ruling of this Circuit in *United States* v. *Caronia*, 703 F.3d 149 (2d Cir. 2012). Plaintiffs are Amarin Pharma, Inc. ("Amarin"), which wants to provide healthcare professionals with truthful, non-misleading information about its prescription drug Vascepa®, and four doctors who want to receive that information, as they determine when and whether to prescribe that drug. If Amarin provides that information, however, it is at high risk of criminal and civil sanctions being sought against it by the United States.

PRELIMINARY STATEMENT

Doctors across America, including Doctor Plaintiffs, prescribe drugs to patients who are at risk of cardiovascular disease and have persistently high triglycerides to lower those patients' triglycerides and/or non-HDL cholesterol.[1] This practice is widespread, medically-accepted, and supported by numerous cardiovascular treatment guidelines and position statements, as well as drug compendia used to determine reimbursability of drugs under federal health care programs.

Amarin's Vascepa®, a prescription drug that consists of pure "EPA" (eicosapentaenoic acid), an omega-3 fatty acid, is one of the drugs often used by doctors who treat patients with persistently high triglycerides. Vascepa® has a safety profile comparable to placebo. It has been shown in a randomized, double-blind, placebo-controlled clinical study to be effective in reducing triglycerides in patients with *very* high triglycerides. In light of this evidence, FDA has approved Vascepa® for treatment of those patients, who are often at risk of pancreatitis and cardiovascular disease.

[1] Triglyceride, like cholesterol, is a type of lipid in the blood. As used herein, the term "high triglycerides" refers to triglyceride levels from 200 mg/dL to 499 mg/dL. The term "very high triglycerides" will refer to triglyceride levels of 500 mg/dL or above. References to the use of drugs to treat patients with "persistently high triglycerides" will refer to the use of these drugs as an adjunct to diet to treat adult patients on statin therapy with mixed dyslipidemia (one or more lipid disorders) and high triglycerides. HDL cholesterol refers to high-density lipoprotein cholesterol, often referred to as "good cholesterol." Non-HDL cholesterol refers to all other kinds of cholesterol.

Amarin also conducted a randomized, double-blind, placebo-controlled clinical study demonstrating that Vascepa® reduces triglycerides (and has other favorable effects) in patients with persistently high triglycerides. FDA does not dispute this study's results. But FDA will not approve Vascepa® for this use without evidence to resolve FDA's newfound uncertainty about whether lowering of triglycerides in these patients will reduce the risk of cardiovascular disease. A study by Amarin to make that determination is underway.

Despite FDA's decision not to approve Vascepa® for treatment of patients with persistently high triglycerides, doctors (including the Doctor Plaintiffs) frequently prescribe Vascepa® to treat such patients to try to further reduce cardiovascular risk. FDA does not dispute that doctors are legally permitted to do so. A substantial percentage (approximately 36-54%) of Vascepa® prescriptions in the U.S. are written for patients with high triglycerides, an "off-label" (i.e., not FDA-approved) use, and many of those patients are believed to have persistently high triglycerides. Indeed, Vascepa® is listed for this use in drug compendia used to determine reimbursement under healthcare programs like Medicare or Medicaid.

Although doctors regularly prescribe Vascepa® for off-label uses, including to treat patients with persistently high triglycerides, FDA regulations forbid Amarin from *promoting* Vascepa® for any off-label use without risk of criminal prosecution under the Food, Drug, and Cosmetic Act ("FDCA") and civil liability under the False Claims Act ("FCA"), even if the information conveyed is truthful and non-misleading.

Amarin disagrees with FDA's decision not to approve Vascepa® for treatment of patients with persistently high triglycerides, but this case does not challenge that decision. Rather, Plaintiffs ask this Court to hold that FDA's prohibitions on "off-label" promotion—as applied to the speech Amarin proposes to make and Doctor Plaintiffs wish to receive—are unconstitutional,

and to declare that Amarin may engage in that speech. Such a holding would fall squarely within this Circuit's ruling in *Caronia*, which held that "speech promoting the lawful, off-label use of an FDA-approved drug" is protected by the First Amendment. 703 F.3d at 169.

The speech Amarin proposes to engage in (*see* pp. 8-9 below) consists of carefully-circumscribed, truthful and non-misleading statements. Amarin wants to inform healthcare professionals such as Doctor Plaintiffs and discuss with them the nature and results of the trial that showed Vascepa®'s effectiveness in lowering triglycerides in patients with persistently high triglycerides. Amarin also wishes to tell these professionals, as dietary supplement manufacturers already tell lay consumers, that supportive but not conclusive research shows that consumption of EPA and DHA omega-3 fatty acids may reduce the risk of coronary heart disease. And Amarin wishes to provide, and Doctor Plaintiffs wish to receive, peer-reviewed scientific publications relevant to the potential effect of EPA on reduction of cardiovascular risk.

To ensure that its speech is not misleading, Amarin would also contemporaneously disclose to healthcare professionals detailed disclaimers, including that (1) FDA has not approved Vascepa® to treat patients with persistently high triglycerides; (2) FDA has not approved Vascepa® to reduce the risk of coronary heart disease; (3) the effect of Vascepa® on the risk of cardiovascular mortality and morbidity has not been determined; and (4) a cardiovascular outcomes study to determine that effect is underway. *See* p. 9 below.

Amarin seeks an order preliminarily enjoining enforcement of FDA regulations against it for engaging in its proposed speech. Amarin has a First Amendment right to engage in such speech (and Doctor Plaintiffs have a First Amendment right to receive it) without fear of (a) criminal prosecution under FDA regulations or (b) civil liability under the FCA. Alternatively, Plaintiffs seek a preliminary injunction because, as-applied, FDA's regulatory regime is

unconstitutionally vague under the Due Process Clause of the Fifth Amendment because it does not fairly notify Amarin of what off-label promotion is permitted and what is forbidden.

STATEMENT OF FACTS

Doctors Prescribe Vascepa® to Lower Triglycerides in Patients with Persistently High Triglycerides

Amarin is a biopharmaceutical company. Ketchum Decl. ¶ 3. Its leading product is Vascepa®, which consists of pure EPA, an omega-3 fatty acid. *Id.* ¶ 5. Vascepa® has a safety profile comparable to a placebo. *Id.* ¶ 8. FDA approved Vascepa® for use as an adjunct to diet to reduce triglycerides in adult patients with very high triglycerides based on a clinical trial conducted by Amarin. *Id.* ¶ 9.

Amarin also conducted a clinical trial demonstrating that Vascepa® is effective in reducing triglycerides in patients with persistently high triglycerides. *Id.* ¶ 12. FDA does not dispute the success of that study but recently advised Amarin that it refuses to approve Vascepa® for treating such patients. *Id.* ¶ 13; Berg Decl. ¶ 11.

Notwithstanding FDA's position, doctors (including the Doctor Plaintiffs) prescribe Vascepa® to patients with high and persistently high triglycerides when they conclude that it is in their patients' best interest. Gottesfeld Decl. ¶ 5; Herbst Decl. ¶ 3; Rishe Decl. ¶ 5; Yung Decl. ¶¶ 6-7; Berg Decl. ¶¶ 6-10. Recent data show that approximately 36% to 54% of Vascepa® prescriptions were for patients with high triglycerides, which includes patients with persistently high triglycerides, each an off-label use. Ketchum Decl. ¶ 17; Berg Decl. ¶¶ 6-10. This prescribing practice is legal, commonplace, and consistent with recommendations in clinical guidelines showing strong links among high triglycerides, high non-HDL cholesterol, and cardiovascular disease. Ketchum Decl. ¶¶ 16-17, 22, 54; Berg Decl. ¶ 3. Doctors prescribe Vascepa® off-label because they believe its potential benefits outweigh its risks, even though the

effect of Vascepa® on heart disease has not yet been definitively determined. Gottesfeld Decl. ¶¶ 4-5; Herbst Decl. ¶ 7; Rishe Decl. ¶ 4; Yung Decl. ¶ 5. Clinical guidelines support that approach. Ketchum Decl. ¶¶ 16, 21, 118-120. As FDA acknowledges:

> [T]he data supporting clinical guidelines is of a different quality than what is required for drug approval by FDA. Clinical guideline development consists of gathering whatever evidence is available, evaluating what data exists, summarizing that data and translating it into a clinical practice guidelines based on opinion. Opinion is used to interpret evidence and also to derive recommendations in the absence of evidence. This can involve values, theory, and clinical experience in deriving the recommendations. This is much different from the regulatory standard for drug approval. . . .

Id. ¶ 119. Use of Vascepa® to treat patients with persistently high triglycerides is also endorsed by recognized medical compendia used by the government to determine whether a drug is "medically accepted" to treat a disease and is thus reimbursable under federal healthcare programs—even though it is not FDA-approved for this use. *Id.* ¶¶ 16, 114.

FDA's Refusal to Approve Vascepa® for Treatment of Patients with Persistently High Triglycerides

In 2008, Amarin approached FDA for guidance on development requirements for FDA approval of an indication for Vascepa® to treat patients with persistently high triglycerides. *Id.* ¶ 63. In 2009, Amarin and FDA entered into an agreement (the "ANCHOR SPA" agreement) under which Amarin would conduct a clinical trial, known as the "ANCHOR" trial, to examine Vascepa®'s effect on patients with persistently high triglycerides. *Id.* FDA reviewed and approved the protocol for the ANCHOR trial in advance and committed that, if the trial met its objectives, the results of the trial would provide the required data for approval of Vascepa® with such patients, subject to narrow statutory bases for rescission. *Id.* ¶ 66.

The ANCHOR trial met all agreed primary and secondary objectives: Vascepa® was effective at lowering triglycerides and had favorable effects on other relevant parameters

(including non-HDL cholesterol lowering) in patients with persistently high triglycerides. *Id.* ¶ 75. Based on these results, in 2013 Amarin applied for expanded FDA approval for use in patients with persistently high triglycerides. *Id.* ¶ 77.

FDA has acknowledged the effects shown in the ANCHOR study. *Id.* ¶ 13. Indeed, in 2012, FDA reflected safety data from the ANCHOR trial in Vascepa®'s approved drug labeling. *Id.* ¶ 84. But FDA purported to rescind the ANCHOR SPA agreement in October 2013, due to what it later termed as its "reevaluation and improved understanding of the relevant scientific knowledge." *Id.* ¶¶ 89-92. According to FDA, reductions of triglycerides in patients with persistently high triglycerides could no longer serve as the primary basis for demonstration of efficacy. *Id.* ¶ 92. Even though Amarin did everything FDA had required to receive approval to treat this new patient population (including spending over $100 million to substantially enroll a required cardiovascular outcomes study), FDA now says it needs additional evidence to resolve FDA's newfound uncertainty about whether the triglyceride-lowering effects of Vascepa® would reduce the risk of cardiovascular disease. *Id.* ¶¶ 69-70, 89-92, 111.

Amarin appealed FDA's decision to purportedly rescind the ANCHOR SPA agreement. *Id.* ¶¶ 91-94. The appeal effort failed; it involved three levels of FDA officials and lasted nearly a year. *Id*. FDA denied the appeals, citing three failed outcomes studies for other drugs that showed that those drugs reduce triglycerides but do not reduce cardiovascular risk more than statins alone. *Id.* ¶ 117. Those studies, however, involved different drugs—fenofibrates and niacin, which work differently than Vascepa® in the body—and did not prospectively focus on patients with persistently high triglycerides. *Id.* at ¶¶ 82-83. FDA nonetheless decided, based on these studies, it would not approve Vascepa® for use in such patients. *Id.* at ¶¶ 99-100. During the appeal process, FDA acknowledged "encouraging" cardiovascular event-lowering effects

seen in an outcomes study of EPA (Vascepa®'s active ingredient) in Japanese patients on statin therapy, while noting that trial's limitations. *Id.* ¶¶ 33-38.

On April 27, 2015, FDA issued to Amarin a Complete Response Letter ("CRL") denying Amarin's request for an indication for persistently high triglycerides. *Id.* ¶ 99. In denying approval for the new indication, the FDA relied on the same three outcomes studies it relied on in support of its decision to purportedly rescind the ANCHOR SPA agreement. *Id.* ¶ 100. FDA noted that those three outcomes studies had been unsuccessful but also acknowledged that data on treated patients with persistently high triglycerides and low HDL-C (or "good" cholesterol) suggested a cardiovascular risk reduction benefit. *Id.* ¶ 117. Accordingly, FDA urged Amarin to advance the Vascepa® outcomes trial to completion, which it is doing. *Id.* ¶¶ 103, 130.

FDA also refused to allow Amarin to use disclaimer language that the effect of Vascepa® on cardiovascular risk has not been determined. *Id.* ¶¶ 95-99. Similar language has been widely employed with other drugs focused on surrogates for cardiovascular risk reduction, such as statins, niacin, fenofibrates and another omega-3 drug. *Id.* ¶¶ 97, 123. The CRL warned Amarin that marketing of Vascepa® for patients with persistently high triglycerides "may be considered to be misbrand[ing]"—and hence criminal—under the FDCA. *Id.* ¶ 105.

FDA's Inconsistent Regulation of Information Concerning Triglyceride-Lowering Claims

For years after the failed outcomes trials of fenofibrates and niacin discussed above, FDA permitted manufacturers of these drugs to promote them for treatment of persistently high triglycerides with disclaimers on their labels stating that they had not been demonstrated to reduce the risk of cardiovascular disease on top of statin therapy. *Id.* ¶¶ 97, 123; Berg Decl. ¶¶ 12-13. Amarin, however, has never been permitted to promote Vascepa® for use in patients with persistently high triglycerides, even though available scientific evidence shows that it may

have additional cardio-protective effects, and even though it has not failed an outcomes trial, and even though it is not associated with certain negative side effects of these drugs. Ketchum Decl. ¶¶ 130-131.

Likewise, for over a decade, FDA has permitted manufacturers that sell dietary supplements containing EPA and/or DHA to tell lay consumers that "[s]upportive but not conclusive research shows that consumption of EPA and DHA omega-3 fatty acids may reduce the risk of coronary heart disease." *Id.* ¶ 132. FDA does not permit Amarin to make that same truthful and non-misleading statement to doctors. *Id.* ¶¶ 150-152. In addition, FDA permits omega-3 supplement manufacturers to make claims that their supplements "lower triglycerides," while Amarin may not make similar claims to healthcare professionals. *Id.* As a result, doctors and consumers have been steered towards omega-3 supplements for treatment of disease instead of Vascepa®. *Id.* ¶¶ 153-157. Dietary supplements are not designed to treat disease, are not subject to strict FDA drug regulations to ensure efficacy, safety, and high manufacturing standards, are lower in omega-3 content, can contain harmful contaminants, are prone to spoilage, and may raise bad cholesterol in high risk patients. *Id.* ¶ 155.

Amarin's Proposed Speech About "Off Label" Use of Vascepa®

Amarin seeks to engage in a dialogue with doctors and other healthcare professionals (including the Doctor Plaintiffs), about the following truthful, non-misleading statements:

- Supportive but not conclusive research shows that consumption of EPA and DHA omega-3 fatty acids may reduce the risk of coronary heart disease.
- The ANCHOR trial demonstrates that Vascepa® lowers triglyceride levels in patients with high (≥ 200 mg/dL and < 500 mg/dL) triglyceride levels not controlled by diet and statin therapy.
- In the ANCHOR trial, Vascepa® 4g/day significantly reduced TG [triglycerides], non-HDL-C [non-high density lipoprotein cholesterol or non-"good cholesterol,"] Apo B [Apolipoprotein B], VLDL-C [very-low-density lipoprotein cholesterol], TC [total

> cholesterol] and HDL-C [high density lipoprotein cholesterol or "good cholesterol"] levels from baseline relative to placebo in patients with high (≥ 200 mg/dL and < 500 mg/dL) triglyceride levels not controlled by diet and statin therapy. The reduction in TG [triglycerides] observed with Vascepa® was not associated with elevations in LDL-C [low-density lipoprotein cholesterol or "bad cholesterol] relative to placebo.

Amarin also seeks to provide healthcare professionals with the following information:

- peer-reviewed scientific publications relevant to the potential effect of EPA on the reduction of the risk of coronary heart disease, including, but not limited to, those listed in Exhibit A to the Complaint. The list is attached as Exhibit A to this brief for the Court's convenience.

- efficacy data from the ANCHOR trial, including, but not limited to, the written statement attached to the Complaint and this brief as Exhibit B.

To ensure that this speech is non-misleading, Amarin would also disclose that:

- FDA has not approved Vascepa® to reduce the risk of coronary heart disease;

- FDA has not approved Vascepa® for the treatment of statin-treated patients with mixed dyslipidemia (one or more lipid disorders) and high (≥ 200 mg/dL and < 500 mg/dL) triglyceride levels;

- The effect of Vascepa® on the risk of cardiovascular mortality and morbidity has not been determined;

- A cardiovascular outcomes study of Vascepa® designed to evaluate the efficacy of Vascepa® in reducing cardiovascular mortality and morbidity in a high risk patient population on statin therapy is currently underway; and

- Vascepa® may not be eligible for reimbursement under government healthcare programs, such as Medicare or Medicaid, to reduce the risk of coronary heart disease or for treatment of statin-treated patients with mixed dyslipidemia and high (≥ 200 mg/dL and < 500 mg/dL) triglyceride levels. We encourage you to check that for yourself.

Id. ¶ 165. Amarin would communicate this information to healthcare professionals through written and digital materials and by engaging in dialogue with them about Vascepa®, peer-reviewed scientific articles, the ANCHOR study, and its results. *Id.* ¶ 166. The message in the written materials, digital media, and dialogue would be guided by and be consistent with the information outlined above and communicated in a truthful and non-misleading manner. *Id.* FDA regulations expose Amarin to criminal liability for engaging in such speech.

FDA Regulations, as Applied, Criminalize Amarin's Proposed Speech

FDA regulations criminalize virtually all off-label promotion by manufacturers to healthcare professionals—truthful or not—including the foregoing speech.

The FDCA prohibits manufacturers from introducing into interstate commerce a non-FDA-approved "new drug" or a drug that is "misbranded," even if it is FDA-approved. 21 U.S.C. §§ 331(a), (d), 352, 355(a). FDA's approval of a new drug extends only to the uses prescribed, recommended, or suggested by the drug's FDA-approved "labeling." 21 U.S.C. § 321(p). The FDCA regulates "labeling" content by prohibiting the introduction of "misbranded" drugs into interstate commerce. A drug is "misbranded" if: (1) "its labeling is false or misleading in any particular"; or (2) the labeling does not bear "adequate directions for use." 21 U.S.C. § 352(a), (f)(1). Violations of the "new drug" and "misbranding" provisions are criminal offenses, subject to imprisonment, and fines and penalties. 21 U.S.C. § 333(a).

The threat of criminal prosecution under the FDCA is a direct result of FDA's interpretation and application of the regulations it has adopted:

First, FDA's expansive definition of "labeling" effectively captures all manufacturer speech concerning off-label prescription drug use. FDA's definition of "labeling" includes any tangible materials distributed by the manufacturer that contain manufacturer-supplied drug information, 21 C.F.R. § 202.1(*l*)(2), precluding a manufacturer from disseminating materials to doctors that contain drug information if those materials prescribe, recommend, or suggest an off-label use of a prescription drug. Based on FDA's application of 21 C.F.R. § 202.1(*l*)(2), the FDCA's prohibition on statements in the "labeling" that are "false or misleading in any particular" extends beyond actually false or misleading statements to any "scientific claims about the safety, effectiveness, contraindications, side effects, and the like regarding prescription

drugs" where FDA has not "had the opportunity to evaluate" those claims (even if supported by scientific research). FDA's interpretation of § 352(a) and redefinition of "labeling" thus effectively precludes manufacturer-supplied drug information not focused on an approved use.

Second, even if information somehow does not constitute "labeling," FDA regulations prohibit discussion of off-label uses of prescription drugs. The FDCA provisions governing prescription drug advertising do not prohibit advertisements for drugs that contain information about off-label uses. 21 U.S.C. § 352(n). FDA, however, has proscribed any "advertisements" that "recommend or suggest any use that is not in the labeling accepted in [the drug's] approved new-drug application," 21 C.F.R. § 202.1(e)(4)(i)(a), effectively prohibiting any direct-to-physician advertisements suggesting off-label uses.

Third, FDA regulations concerning the FDCA's misbranding provisions also restrain manufacturer speech. As noted above, the FDCA deems a drug "misbranded" if the drug's labeling lacks "adequate directions for use." 21 U.S.C. § 352(f)(1).[2] Under FDA regulations, for a prescription drug to avoid being misbranded, its labeling must have sufficient directions for "the purposes for which [the drug] is intended, including all purposes for which [the drug] is advertised or represented." 21 C.F.R. § 201.100(c)(1). Any representations made by a manufacturer concerning its prescription drug that do not directly focus on the drug's on-label use will be considered by FDA an "intended" use for which the manufacturer must provide "adequate information," consisting of "indications, effects, dosages, routes, methods, and frequency and duration of administration, and any relevant hazards, contraindications, side effects, and precautions." *Id.* By definition, FDA-approved labeling does not include information about off-label uses. *Id.* at § 201.100(c)(2). Thus, FDA considers any drug that is

[2] FDA later clarified that for prescription drugs, the "labeling on or within the package from which the drug is to be dispensed" must bear "adequate *information* for its use." 21 C.F.R. § 201.100(c)(1).

"advertised or represented" for an off-label use to violate the "adequate information" provision and to be "misbranded" and subject to criminal sanctions.[3]

The False Claims Act

The government's interpretation of the FCA also exposes manufacturers to potential civil liability for engaging in truthful and non-misleading off-label promotion to doctors.

Under the FCA, any person who has knowingly "cause[d] to be presented a false or fraudulent claim for payment of approval" or who has knowingly made or caused to be made "a false record or statement material to a false or fraudulent claim" to the government must pay a civil penalty between five and ten thousand dollars and "3 times the amount of damages which the Government sustains because of the act of that person." 31 U.S.C. § 3729(a)(1).

Federal health care programs generally cover drugs for medically-accepted indications. Ketchum Decl. ¶ 114. Medically-accepted indications not only include those listed on an FDA-approved label but also include certain off-label indications supported by a citation in an approved drug compendium if certain other conditions are met. *See generally* 42 U.S.C. § 1396r-8(k)(6) (Medicaid); *id.* at § 1395x(t)(2)(B) (Medicare). Under the government's view, "when a manufacturer engages in the marketing of drugs for indications that are not FDA approved for that drug or not otherwise supported by a compendium listing, its conduct may cause false non-covered claims to be submitted to federal health care programs, and liability under the FCA may lie." *See* Kurtzberg Decl. Ex. 9 (*United States ex rel. Matthew Cestra* v. *Cephalon, Inc.*, 10 Civ. 6457 (SHS), Statement of Interest, ECF No. 83 at 2-3 (S.D.N.Y. Nov. 7,

[3] In addition to criminal liability, enforcement actions can also involve civil remedies including disgorgement and civil restitution for alleged violations of the FDCA. *See* 21 U.S.C. § 332(a); Kurtzberg Decl. Ex. 1 (Press Release, Department of Justice, *Johnson & Johnson to Pay More than $2.2 Billion to Resolve Criminal and Civil Investigations* (Nov. 4, 2013) ("J&J Settlement Release") (summarizing settlement involving civil payments and criminal fines and forfeiture).)

2013) ("*Cestra* Statement")).[4] Thus, according to the government, so long as statements that can be characterized as "marketing" are made by a drug company about the off-label use of a product, the company it is at risk because—without more—it may thereby "cause" the purchaser of drugs to seek non-covered reimbursement.

As discussed above, Vascepa® does not currently have an approved indication from FDA for use to reduce coronary heart disease or triglycerides in patients with persistently high triglycerides, but it is supported by a medical compendium listing Vascepa® for use by such patients. Ketchum Decl. ¶ 115. Although Vascepa® is likely reimbursable under federal healthcare programs when prescribed to such patients, there may be certain circumstances in which it does not meet specific state or federal requirements. *Id.* ¶ 116. In an abundance of caution, Amarin's proposed speech includes a disclaimer stating that (a) Vascepa® has not been approved by FDA to reduce coronary heart disease or for treatment of patients with persistently high triglycerides and (b) Vascepa® may not be eligible for reimbursement under federal healthcare programs, such as Medicare and Medicaid, for such uses. *Id.* ¶ 165. It also encourages doctors to "check for themselves" whether such reimbursement is appropriate under applicable laws. *Id.*

Recent action by the government illustrates that Amarin risks civil liability if it engages in its proposed speech about Vascepa®. The government filed the *Cestra* Statement in an action in this Court against a manufacturer for the alleged off-label promotion of two drugs, after the drug's recipient submitted false claims for reimbursement of those drugs.

[4] *See, e.g.*, *Strom ex rel. United States* v. *Scios, Inc.*, 676 F. Supp. 2d 884, 886 (N.D. Cal. 2009) (government alleged defendants violated FCA where "Defendants induced doctors to prescribe their drug . . . for a use that was not medically accepted").

The government reiterated its position last year in another case in which a drug manufacturer distributed reprints of medical studies published in independent and highly-respected journals such as *Cardiology* and the *American Heart Journal* and forwarded letters summarizing the results of clinical trial results of its product. *See* Kurtzberg Decl. Ex. 5 (*United States ex rel. Frank Solis* v. *Millennium Pharmaceuticals, Inc.*, 09 Civ. 3010, Second Amended Complaint at ¶¶ 49-56, ECF No. 107 (MCE JFM) (E.D. Cal. 2014).) According to the statement of interest filed by the government in that case, so long as it was "reasonably foreseeable" that those statements about off-label uses of its product might "influence the submissions of th[e] false claims," liability could be imposed on the manufacturer, even if not a word that it said about its product was false. *See* Kurtzberg Decl. Ex. 6 (*United States ex rel. Frank Solis* v. *Millennium Pharmaceuticals, Inc.*, 09 Civ. 3010, Statement of Interest at 9, ECF No. 120 (MCE JFM) (E.D. Cal. 2014).)

The government's position is thus that Amarin could violate the FCA by distributing to doctors materials that truthfully and non-misleadingly discuss off-label use of Vascepa® if those doctors wrote prescriptions for off-label use to patients who submitted claims to Medicare or Medicaid. Further, if Amarin engages in this off-label promotion, it risks being sued under the FCA by either the government or by private *qui tam* plaintiffs. *See* 31 U.S.C. § 3730(b). The government and private plaintiffs have brought numerous FCA actions based on off-label promotion.[5] Because the FCA provides for treble damages, many pharmaceutical manufacturers have settled such suits, often for amounts in the hundreds of millions, or even billions, of dollars.

[5] *See* Kurtzberg Decl. Ex. 1 (J&J Settlement Release (civil settlements with federal government and states for alleged off-label promotion totaling $1.72 billion)); *id.* at Ex. 2 (Press Release, Department of Justice, *Justice Department Announces Largest Health Care Fraud Settlement in Its History* (Sept. 2, 2009) (Pfizer paid $1 billion to resolve FCA claims)); *id.* at Ex. 3 (Press Release, Department of Justice, *Pharmaceutical Companies to Pay $214.5 Million to Resolve Allegations of Off-label Promotion of Zonegran* (Dec. 15, 2010) (over $100 million to resolve civil allegations under the FCA)); *id.* at Ex. 4 (Press Release, Department of Justice, *Novartis Vaccines &*

ARGUMENT

To obtain a preliminary injunction, Plaintiffs must establish that they are likely to succeed on the merits, that they are likely to suffer irreparable harm absent preliminary relief, that the balance of equities tips in their favor, and that an injunction is in the public interest. *Winter* v. *Natural Res. Def. Council, Inc.*, 555 U.S. 7, 20 (2008). Because Plaintiffs seek an injunction that will alter the status quo, they must show a "substantial" likelihood of success on the merits. *New York Progress & Prot. PAC* v. *Walsh*, 733 F.3d 483, 486 (2d Cir. 2013).

I. PLAINTIFFS ARE SUBSTANTIALLY LIKELY TO SUCCEED ON THE MERITS

Plaintiffs are substantially likely to establish that FDA regulations prohibiting off-label promotion fail First Amendment scrutiny, or are impermissibly vague, as applied in this case. Plaintiffs are also substantially likely to establish that the government's interpretation of the FCA fails First Amendment scrutiny as applied in this case.[6]

a. FDA's off-label promotion ban violates Plaintiffs' First Amendment rights

"[S]peech in aid of pharmaceutical marketing," the Supreme Court has stated, "is a form of expression protected by the Free Speech clause of the First Amendment." *Sorrell* v. *IMS Health Inc.*, 131 Sup. Ct. 2653, 2659 (2011). A party seeking to uphold a restriction on commercial speech carries the burden of justifying it, *Thompson* v. *W. States Med. Ctr.*, 535

Diagnostics to Pay More Than $72 Million to Resolve False Claims Act Allegations Concerning TOBI (May 4, 2010)); Stephanie M. Greene & Lars Noah, *Off-Label Drug Promotion and the First Amendment*, 162 U. PA. L. Rev. Online 239, 265 (2014) (plaintiffs "have repeatedly pointed to off-label promotion as a basis for triggering prosecution even where the FDA later approved some of these uses").

[6] Amarin's claims are suitable for judicial review. Exhaustion is not required where "irreparable injury may occur without immediate judicial relief." *Able* v. *United States*, 88 F.3d 1280, 1288 (2d Cir. 1996). Here, Amarin asserts FDA regulations restrict its speech. Under such circumstances, irreparable harm is presumed. *Bronx Household of Faith* v. *Bd. of Educ. of City of New York*, 331 F.3d 342, 349 (2d Cir. 2003). Further, Amarin's claims raise a "substantial constitutional question." *Able*, 88 F.3d at 1288 ("[W]hen constitutional questions are in issue, the availability of judicial review is presumed.") (citation omitted). Plaintiffs' claims are also ripe. *See* 13B Charles A. Wright & Arthur R. Miller, Fed. Prac. & Proc. § 3532.3 (3d ed. 2008) ("First Amendment rights of free expression and association are particularly apt to be found ripe for immediate protection, because of the fear of irretrievable loss.").

U.S. 357, 373 (2002), and a criminal regulatory scheme prohibiting commercial speech like the one at issue here warrants particularly heightened scrutiny. *Caronia*, 703 F.3d at 163.[7]

The *Caronia* decision is directly on point and establishes that Plaintiffs are likely to succeed on the merits of their claim that FDA's promotion ban violates the First Amendment.

i. Off-label promotion is protected speech

In what has been described as a "watershed decision,"[8] *Caronia* held that under the First Amendment the government may not prohibit or punish "speech promoting the lawful, off-label use of an FDA-approved drug." 703 F.3d at 169. The prescription drug at issue in *Caronia* was Xyrem. *Id.* at 155. Xyrem has dangerous side effects, including coma and death; its active ingredient is known colloquially as the "date rape drug." *Id.* Although FDA approved Xyrem to treat narcolepsy, it required Xyrem's labeling to include a "black box" warning reflecting that the drug's safety and efficacy were not established in children and that "the drug had 'very limited' experience among elderly patients." *Id.* The government prosecuted Caronia, a pharmaceutical sales representative, for conspiring to engage in "misbranding" after he told a doctor (a government cooperator) off-label information: that Xyrem was a "very safe drug" that could treat conditions such as Parkinson's disease and had been used by patients "greater than sixty-five" and "as young as fourteen." *Id.* at 156-57. Before trial, the district court held that

[7] Plaintiffs recognize that *Central Hudson*'s intermediate scrutiny standard controls here but reserve the right to argue that strict scrutiny applies. There is no "basis in the First Amendment for the relaxed scrutiny [the Supreme] Court applies to laws that suppress nonmisleading commercial speech." *Milavetz, Gallop & Milavetz, P.A.* v. *United States*, 559 U.S. 229, 255 (2010) (Thomas, J., concurring in part and concurring in the judgment).

[8] Michael Walsh, *Trying to Infuse Common Sense Into Parallel Claims and Off-Label Promotion*, mondaq.com (May 12, 2015) (*Caronia* is a "watershed decision."); *see also* Katie Thomas, *Ruling is Victory for Drug Companies in Promoting Medicine for Other Uses*, N.Y. Times (Dec. 3, 2012) (quoting former FDA chief counsel as describing *Caronia* as "very significant."); John T. Bentivoglio, et al., *How Caronia Could Reshape Government Investigations*, Law360 (Jan. 1, 2013) (describing *Caronia* as a "watershed event."); Peter G. Neiman, et al., *Revisiting 'Off-Label' Drug Promotion Resolutions in Light of 'Caronia*,' N.Y.L.J (Feb. 28. 2013) ("Caronia has cast serious doubt on the government's theory criminalizing off-label promotion."); Alison Frankel, *Why U.S. is Forgoing Appeal of Landmark 2nd Circuit Off-label Ruling*, Reuters.com (Jan. 24, 2013) (Caronia is a "landmark" ruling); David Frum, *Drug Industry's Free Speech Helps Doctors*, CNN.com (Dec. 10, 2012) (*Caronia* "abruptly changed" the rule prohibiting pharmaceutical companies from discussing off-label use).

FDA's restriction on off-label promotion passed constitutional muster under the commercial speech doctrine. *Id.* at 158.

The Second Circuit reversed. It "decline[d] to adopt the government's construction of the FDCA's misbranding provisions to prohibit manufacturer promotion alone." *Id.* at 168. Doing so "would unconstitutionally restrict free speech." *Id.* The *Caronia* court applied *Central Hudson*'s test for determining whether commercial speech deserves First Amendment protection. That test requires evaluation of whether: (1) the speech concerns lawful activity and was not misleading; (2) the asserted government interest is substantial; (3) the regulations at issue directly advance the asserted government interest to a material degree; and (4) whether the regulations are narrowly drawn and not more extensive than necessary to serve the asserted interest. *Id.* at 164 (citing *Central Hudson Gas & Elec. Corp.* v. *Pub. Serv. Comm'n of N.Y.*, 447 U.S. 557, at 566 (1980)). The *Caronia* court found the first and second *Central Hudson* factors "easily" met: the promotion of off-label drugs was "not in and of itself false or misleading" and concerned lawful activity, and the government had an asserted interest in drug safety and the public health. *Id.* at 165-66.

As to the third *Central Hudson* factor, the *Caronia* court concluded that FDA's prohibition on off-label promotion was not narrowly drawn to directly advance the government's interests, but rather provided "only ineffective or remote support" for that interest:

> In effect, even if pharmaceutical manufacturers are barred from off-label promotion, physicians can prescribe, and patients can use, drugs for off-label purposes. . . . As off-label drug use itself is not prohibited, it does not follow that prohibiting the truthful promotion of off-label drug usage by a particular class of speakers would directly further the government's goals of preserving the efficacy and integrity of the FDA's drug approval process and reducing patient exposure to unsafe and ineffective drugs.
>
> [FDA's prohibition] "paternalistically" interferes with the ability of physicians and patients to receive potentially relevant treatment information; such barriers to

> information about off-label use could inhibit, to the public's detriment, informed and intelligent treatment decisions.

Id. at 166-67 (internal citations and quotation marks omitted).[9] Finally, FDA's "complete and criminal ban on off-label promotion" was "more extensive than necessary to achieve the government's substantial interests." *Id.* at 167. "Numerous" less speech-restrictive alternatives were available to the government, including (1) directly regulating off-label drug use, (2) providing guidance that differentiates between misleading and false promotion, exaggerations and embellishments, and truthful or non-misleading information; (3) developing a warning or disclaimer system; (4) developing different "safety tiers" for off-label drugs; (5) creating ceilings or caps on off-label prescriptions; and (6) prohibiting certain dangerous off-label uses altogether. *Id.* at 167-68. Quoting the Supreme Court, the Second Circuit held that "[i]f the First Amendment means anything, it means that regulating speech must be a last—not first—resort, *Thompson*, 535 U.S. at 373. . . . The government's interests could be served equally well by more limited and targeted restrictions on speech." *Caronia*, 703 F.3d at 168.

ii. Amarin's proposed speech is protected under the First Amendment

Caronia establishes that Amarin is substantially likely to succeed on the merits of its First Amendment challenge to the FDA regulations *Caronia* held were subject to heightened scrutiny.

As to prong one of *Central Hudson*, *Caronia* established that off-label promotion concerns lawful activity and is not inherently "in and of itself false or misleading." 703 F.3d at 165. The speech Amarin proposes to engage in (*see* pp. 8-9 above) consists of carefully-circumscribed, truthful, and non-misleading statements. Amarin wishes to engage in a dialogue guided by and consistent with these statements with Doctor Plaintiffs and other healthcare

[9] *Caronia*'s rejection of governmental "paternalism" finds support in several seminal Supreme Court commercial speech cases. *See Caronia,* 703 F.3d at 166 (quoting *Va. State Bd. of Pharmacy* v. *Va. Citizens Consumer Council, Inc.*, 425 U.S. 748, 770 (1976); *44 Liquormart, Inc.* v. *Rhode Island*, 517 U.S. 484, 503 (1996); *Sorrell*, 131 S. Ct. at 2670-71).

professionals. To ensure these truthful statements are not misleading, Amarin would contemporaneously convey disclaimers about Vascepa®'s limitations. *Id.* Amarin's proposed speech satisfies the first *Central Hudson* factor.

As to prongs two, three, and four of *Central Hudson*, *Caronia*'s reasoning is similarly directly on point. Amarin does not dispute *Caronia*'s conclusion that there is a substantial government interest in advancing public health under the second *Central Hudson* factor. 703 F.3d at 166. But, as in *Caronia*, FDA's limitations on and threats to off-label speech, as applied here, paternalistically hinder, rather than advance, its asserted interest in advancing public health. In the market for triglyceride-lowering drugs, FDA's regulations have actually served to *mislead* doctors about their options, having permitted for years some speech about triglyceride-lowering drugs but prohibiting other speech. Berg Decl. ¶¶ 11-19. The effect of that disparity is particularly concerning given that drugs for which speech was freely permitted, fenofibrates and niacin, had failed outcomes studies (Vascepa® has not) and had more serious negative side effects than Vascepa®. *Id.* at ¶ 13; Ketchum Decl. ¶¶ 121, 123. It is also concerning given that FDA-approved labeling allowed the manufacturer of Lovaza®, a drug that contains EPA and DHA, to tell healthcare professionals that Lovaza® is effective in lowering triglycerides in patients with persistently high triglycerides, even though FDA denied approval to Lovaza® after a study evaluating the effects of the drug also showed that it unacceptably raised LDL-C (i.e., "bad" cholesterol). Berg Dec. ¶¶ 14-16; Ketchum Decl. ¶¶ 125-126. And it is also concerning given that FDA permits supplement manufacturers in the loosely-regulated dietary supplement industry to make qualified health claims about the state of the research on omega-3 fatty acids but prohibits Amarin from doing the same. Ketchum Decl. ¶ 150. FDA's regulations therefore operate to *prevent* doctors and patients from learning about a potentially better treatment option.

Similarly, FDA's interest in reducing exposure to unsafe or ineffective drugs is hardly advanced by permitting manufacturers in the loosely-regulated dietary supplement industry to provide qualified health claims about the state of the research on omega-3 fatty acids and make prominent claims that their products reduce triglycerides, while prohibiting Amarin from making the same truthful claims about Vascepa®.

Finally, Amarin's proposed disclaimers are a far less speech-restrictive alternative to the government's outright ban on Amarin's speech about Vascepa®,[10] as are any of "numerous" measures identified in *Caronia*. 703 F.3d at 167-68; *see* p. 9 above. FDA cannot permit doctors to prescribe approved drugs like Vascepa® freely for off-label uses, and then prohibit drug manufacturers, like Amarin, from speaking truthfully to them about such uses. "The government's construction of the FDCA essentially legalizes the outcome—off-label use—but prohibits the free flow of information that would inform that outcome." *Caronia*, 703 F.3d at 167. Under the First Amendment, this gets things backwards. "[R]egulating speech must be a last—not first—resort." *Thompson*, 535 U.S. at 373; *Caronia*, 703, F.3d at 168.

iii. FDA regulations improperly burden Doctor Plaintiffs' First Amendment rights

Doctor Plaintiffs are also substantially likely to succeed on the merits of their First Amendment challenge to FDA regulations. The First Amendment protects the right to receive commercial speech. *See Sorrell*, 131 S. Ct. at 2664 ("A consumer's concern for the free flow of commercial speech often may be far keener than his concern for urgent political dialogue.") (citation and internal quotation marks omitted); *see also Va. State Bd. of Pharmacy*, 425 U.S. at

[10] *See Thompson*, 535 U.S. at 376 (interest in preventing misleading ads "could be satisfied by the far less restrictive alternative of requiring each compounded drug to be labeled with a warning that the drug had not undergone FDA testing and that its risks were unknown.").

756 ("[W]here a speaker exists, as is the case here, the protection afforded is to the communication, to its source and to its recipients both").

FDA's off-label promotion ban infringes the Doctor Plaintiffs' First Amendment rights because they cannot receive truthful and non-misleading information about the risks and benefits of Vascepa® to make fully-informed medical decisions for their patients. Such information is essential to doctors. Since Vascepa® is listed for treatment of patients with high triglycerides in the medical compendia used by the government to determine reimbursability under federal healthcare programs, Ketchum Decl. ¶ 115, use of Vascepa® to treat patients with persistently high triglycerides has effectively been deemed by the government to be "medically accepted."[11] Doctors believe, understandably, that Amarin is the expert on its own product and is in the best position to provide information about it. Gottesfeld Decl. ¶ 11; Herbst Decl. ¶ 11; Yung Decl. ¶ 11. FDA regulations therefore operate to harm Doctor Plaintiffs, and in turn their patients, each day that Amarin cannot discuss off-label use of Vascepa® with them.

b. FDA's off-label promotion ban violates Amarin's Fifth Amendment rights

FDA regulations permit *no* off-label promotion, no matter how truthful or non-misleading. Even FDA's non-binding "Guidance" on the issue[12]—which permits drug manufacturers to respond to unsolicited questions from doctors about off-label uses (but not to do so otherwise)—does not acknowledge that any off-label promotion is legal, but simply says

[11] *See, e.g.*, 42 U.S.C. § 1395x(t)(2)(B). Under this Medicare provision, for a drug to qualify for reimbursement, it must be provided for a "medically accepted indication." *Id.* Medically accepted indications include both uses approved by the FDA *and* off-label uses supported by one or more recognized compendia. *Id.* at § 1395x(t)(2)(B)(i)-(ii). Vascepa® is listed in such a compendium and is therefore deemed by the government to be "medically accepted." Ketchum Decl. ¶ 115 (Am. Hosp. Formulary Serv.—Drug Information at 1 (icosapent ethyl (Vascepa®) "used to reduce residually high (200-499 mg/dL) triglyceride concentrations in statin-treated adults at high risk for cardiovascular disease despite adequately controlled LDL-cholesterol concentrations (40-99 mg/dL)").); *see also* 1396r-8(k)(6) (Medicaid).

[12] FDA, *Draft Guidance for Industry Responding to Unsolicited Requests for Off-Label Information About Prescription Drugs and Medical Devices*, 2011 WL 7029653, at 2 (Dec. 2011).

FDA has no present intent to prosecute what, under FDA's interpretation of the law, is illegal. *Caronia* is directly at odds with FDA's view of the law: it holds that truthful and non-misleading commercial speech intending to promote drugs for off-label use is protected under the First Amendment. But since *Caronia*, FDA has done nothing to clarify what off-label promotion, if any, is legally permitted. The resulting uncertainty has had a chilling effect on the entire industry. Ketchum Decl. ¶ 168; Berg Decl. ¶ 20. Given that the stakes of crossing the proverbial line are so high (potential jail time and massive fines), drug companies like Amarin are forced to err on the side of caution and refrain from engaging in off-label promotion altogether. Ketchum Decl. ¶ 168. This lack of clarity is unacceptable under the Due Process Clause of the Fifth Amendment, which requires "fair notice of what is prohibited." *FCC* v. *Fox Television Stations*, 132 S. Ct. 2307, 2317 (2012).

In the wake of *Caronia*, a representative of the Office of Prescription Drug Promotion (an FDA sub-entity) issued the following statement in seeking to explain why the United States was not seeking a writ of certiorari from such a consequential ruling:

> FDA does not believe that the *Caronia* decision will significantly affect the agency's enforcement of the drug misbranding provisions of the [FDCA]. . . . Because the court did not address the constitutionality of a prosecution resting on [a misbranding] theory, and because the court also acknowledged that the First Amendment does not preclude an enforcement action based on speech regarding unapproved uses that is false or misleading, the Second Circuit's decision does not bar the government from continuing to enforce the misbranding provisions of the [FDCA], including through criminal prosecution where appropriate, in cases involving off-label promotion.

See Kurtzberg Decl. Ex. 7 (Jill Wechsler, *Tom Abrams:* Caronia *Won't Stop Off-Label Enforcement*, PHARMEXEC.COM (Jan. 29, 2013).) That position is a startling one. It is true that *Caronia* has not significantly affected FDA's enforcement of the law. But it should have had just that effect. And it is also true that *Caronia* does not bar all prosecutions based on

misbranding. But it *does* bar the government from continuing to enforce the FDCA's misbranding provisions in cases of truthful and non-misleading off-label promotion. As the *Caronia* court held: "even if speech can be used as evidence of a drug's intended use, we decline to adopt the government's construction of the FDCA's misbranding provisions to prohibit manufacturer promotion alone as it would unconstitutionally restrict free speech. We construe the misbranding provisions of the FDCA as not prohibiting and criminalizing the truthful off-label promotion of FDA-approved prescription drugs." 703 F.3d at 168.

FDA's position leaves Amarin and other drug manufacturers in the dark about what they may or may not say. FDA has received requests for guidance on the limits of acceptable off-label promotion,[13] but it has not reconciled its approach to off-label promotion with *Caronia* or clarified to manufacturers what speech it believes is permitted or prohibited. Such uncertainty is "particularly treacherous" in a case such as this, where criminal penalties "deter those who seek to exercise protected First Amendment rights." *Buckley* v. *Valeo*, 424 U.S. 1, 76-77 (1976).

c. The government's interpretation of the FCA fails First Amendment scrutiny

Like the FDCA, the FCA does not facially prohibit Amarin from promoting off-label use of Vascepa®. The government's position that the FCA can be used to punish a manufacturer's truthful speech about off-label use that may "influence" the submission of a false claim for payment to the government imperils that speech.

The government's reading of the FCA results in an overly-expansive, on-the-ground prohibition on protected speech that cannot begin to satisfy *Central Hudson* or *Caronia* scrutiny.

[13] For example, the Medical Information Working Group ("MIWG") submitted a petition, citing other similar petitions, requesting that FDA "take further steps to reevaluate, and modify as necessary, the Agency's regulations and policies with respect to manufacturer dissemination of new-use information in light of public health considerations, statutory limitations, and recent First and Fifth Amendment case law." *See* Kurtzberg Decl. Ex. 8 (MIWG, Citizen Petition, Docket No. FDA-2013-P-1079, at 2 (Sept. 3, 2013).)

The *Central Hudson* test as applied to the government's position regarding the FCA mirrors the analysis in Section I.a. above concerning FDA's ban on off-label promotion.

Far from misleading doctors into causing false claims submissions, Amarin's proposed speech warns doctors that: "Vascepa® may not be eligible for reimbursement under government healthcare programs, such as Medicare or Medicaid, to reduce the risk of coronary heart disease or for treatment of statin-treated patients with mixed dyslipidemia and high (≥ 200 mg/dL and < 500 mg/dL) triglyceride levels. We encourage you to check that for yourself." *See* p. 9 above. It is inconceivable how barring Amarin from engaging in its proposed speech that includes a "belt and suspenders" disclaimer reminding doctors to prescribe reimbursable drugs advances the government's interest in deterring false claims. *See* Kurtzberg Decl. Ex. 9 (*Cestra* Statement at 4 (acknowledging that "for FCA cases predicated on off-label drug marketing, the central question is whether the defendant's marketing caused the submission of false claims, i.e., claims for off-label uses that are not covered or reimbursable by federal health care programs").) This disclaimer is a less speech-restrictive alternative to the government's position that all off-label speech must be stifled to deter false claims. *See Thompson*, 535 U.S. at 376.

II. PLAINTIFFS WILL SUFFER IRREPARABLE INJURY ABSENT A PRELIMINARY INJUNCTION

With regard to the irreparable injury prong of the preliminary injunction analysis, Judge Koeltl recently summed up the law as follows:

> In a case alleging a First Amendment deprivation, if the plaintiffs show a substantial likelihood that their First Amendment rights are being violated, the "irreparable harm" prong of the preliminary injunction standard is met, because the "'loss of First Amendment freedoms, for even minimal periods of time, unquestionably constitutes irreparable injury.'" *N.Y. Magazine* v. *Metro. Transp. Auth.*, 136 F.3d 123, 127 (2d Cir.1998) (quoting *Deeper Life Christian Fellowship, Inc.* v. *Board of Educ.*, 852 F.2d 676, 679 (2d Cir.1988); *see also Elrod* v. *Burns*, 427 U.S. 347, 373 (1976); *New York Progress & Prot. PAC* v. *Walsh*, 733 F.3d 483, 488 (2d Cir. 2013) ("When a party seeks a preliminary

> injunction on the basis of a potential First Amendment violation, the likelihood of success on the merits will often be the determinative factor.")

Am. Freedom Def. Initiative v. *Metro. Transp. Auth.*, No. 14 CV. 7928 JGK, 2015 WL 1775607, at *5 (S.D.N.Y. Apr. 20, 2015). This Court presumed irreparable harm in a similar action involving speech restrictions. *Am. Freedom Def. Initiative* v. *Metro. Transp. Auth.*, 880 F. Supp. 2d 456, 465 (S.D.N.Y. 2012). Plaintiffs have shown a substantial likelihood of success that their First Amendment rights are being violated by FDA's prohibition on off-label promotion and are therefore entitled to a finding of irreparable harm.

III. A PRELIMINARY INJUNCTION IS IN THE PUBLIC INTEREST

The balance of equities and the public interest also support preliminary relief where, as here the moving party is likely to succeed on the merits of their First Amendment challenge.[14] That is because the "[g]overnment does not have an interest in the enforcement of an unconstitutional law." *New York Progress and Prot. PAC*, 733 F.3d at 488. Rather, as the Supreme Court also observed in *Sorrell*, "securing First Amendment rights is in the public interest." *Id.* Especially so here since "in the fields of medical and public health, 'where information can save lives,' it only furthers the public interest to ensure that decisions about the use of prescription drugs, including off-label usage, are intelligent and well-informed." 131 S. Ct at 2664. A physician quoted by the Supreme Court put it this way: "We have a saying in medicine, information is power. And the more you know, or anyone knows, the better decisions can be made." *Sorrell*, 131 S. Ct. at 2671.

CONCLUSION

The motion for a preliminary injunction should be granted.

[14] The balance of the equities and public interest factors "merge when the Government is the opposing party." *Nken* v. *Holder*, 556 U.S. 418, 420 (2009).

Dated: New York, New York
May 22, 2015

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EXHIBIT A

Representative Sample of Peer Reviewed Scientific Publications Relevant to the Potential Effect of EPA on the Reduction of the Risk of Coronary Heart Disease

Bays H, Ballantyne C, Braeckman R, et al. Icosapent ethyl, a pure ethyl ester of eicosapentaenoic acid: effects on circulating markers of inflammation from the MARINE and ANCHOR studies. *Am J Cardiovasc Drugs*. 2013;13:37-46.

Doi M, Nosaka K, Miyoshi T, et al. Early eicosapentaenoic acid treatment after percutaneous coronary intervention reduces acute inflammatory responses and ventricular arrhythmias in patients with acute myocardial infarction: a randomized, controlled study. *Int J Cardiol.* 2014:176(3):577-582.

Harris W. Are n-3 fatty acids still cardioprotective? *Curr Opin Clin Nutr Metab Care*. 2013;16(2):141-149.

Matsuzaki M, Yokoyama M, Saito Y, et al. Incremental effects of eicosapentaenoic acid on cardiovascular events in statin-treated patients with coronary artery disease. *Circ J.* 2009;73:1283-1290.

Mozaffarian D, Lemaitre RN, King IB, et al. Plasma phospholipid long-chain omega-3 fatty acids and total and cause-specific mortality in older adults: the cardiovascular health study. *Ann Intern Med*. 2013;158(7):515-525.

Mozaffarian D, Wu JHY. Omega-3 Fatty Acids and Cardiovascular Disease. *J Am Coll Cardiol*. 2011;58(20):2047-2067.

Saito Y, Yokoyama M, Origasa H, et al. Effects of EPA on coronary artery disease in hypercholesterolemic patients with multiple risk factors: sub-analysis of primary prevention cases from the Japan EPA Lipid Intervention Study (JELIS). *Atherosclerosis*. 2008;200:135-140.

Takaki A, Umemoto S, Ono K, et al. Add-on therapy of EPA reduces oxidative stress and inhibits the progression of aortic stiffness in patients with coronary artery disease and statin therapy: a randomized controlled study. *J Atheroscler Thromb.* 2011;18:857-866.

Thies F, Garry JMC, Yaqoob P, et al. Association of n-3 polyunsaturated fatty acids with stability of atherosclerotic plaques: a randomized controlled trial. *Lancet*. 2003;361:477-485.

Ueeda M, Doumei T, Takaya Y, et al. Serum n-3 polyunsaturated fatty acid levels correlate with the extent of coronary plaques and calcifications in patients with acute myocardial infarction. *Circ J.* 2008;72:1836-1843.

Vecka M, Dusejovska M, Stankova B, et al. N-3 polyunsaturated fatty acids in the treatment of atherogenic dyslipidemia. *Neuroendocrinol Lett.* 2012;33(Suppl. 2):87-92.

Wu JHY, Mozaffarian D. Omega-3 fatty acids, atherosclerosis progression and cardiovascular outcomes in recent trials: new pieces in a complex puzzle. *Heart.* 2014;100(7):530-533.

Yokoyama M, Origasa H, Matsuzaki M, et al. Effects of eicosapentaenoic on major coronary events in hypercholesterolaemic patients (JELIS): a randomised open-label, blinded endpoint analysis. *Lancet.* 2007;369:1090-1098.

EXHIBIT B

Co-administration Therapy with Statins for Additional Lipid Management in Mixed Dyslipidemia

The effects of VASCEPA as add-on therapy to treatment with statins were evaluated in a randomized, placebo-controlled, double-blind, parallel-group study of 453 adult patients (226 on VASCEPA and 227 on placebo) with persistent high triglyceride levels (≥200 mg/dL and <500 mg/dL) despite statin therapy. All patients were receiving statin therapy (atorvastatin, rosuvastatin, or simvastatin) and were treated to LDL-C goal prior to randomization. Patients were randomized to either VASCEPA or placebo and treated for 12 weeks with statin co-therapy. The same statin at the same dose was continued throughout the study. The median baseline TG and LDL-C levels in these patients were 259 mg/dL and 83 mg/dL, respectively. The randomized population in this study was mostly Caucasian (96%) and male (61%). The mean age was 61 years and the mean body mass index was 35 kg/m^2. Seventy-three percent (73%) of patients had diabetes at baseline.

The changes in the major lipoprotein lipid parameters for the groups receiving VASCEPA plus statin or placebo plus statin are shown in the following table:

Response to the Addition of VASCEPA to Ongoing Statin Therapy in Patients with High Triglyceride Levels (≥200 mg/dL and <500 mg/dL)

Parameter	Vascepa 4 g/day + Statin N=226		Placebo + Statin N=227		Difference (95% Confidence Interval)	p-value
	Baseline	% Change	Baseline	% Change		
TG (mg/dL)	265	-18	259	6	-22 (-27, -16)	<0.0001
LDL-C (mg/dL)	82	2	84	9	-6 (-11, -2)	<0.01
Non-HDL-C (mg/dL)	128	-5	128	10	-14 (-17, -10)	<0.0001
Apo B (mg/dL)	93	-2	91	7	-9 (-12, -6)	<0.0001
VLDL-C (mg/dL)	44	-12	42	15	-24 (-32, -17)	<0.0001
TC (mg/dL)	167	-3	168	9	-12 (-15, -9)	<0.0001
HDL-C (mg/dL)	37	-1	39	5	-5 (-7, -2)	<0.01

% Change= Median Percent Change from Baseline
Difference= Median of [VASCEPA % Change – Placebo % Change] (Hodges-Lehmann Estimate)
p-values from Wilcoxon rank-sum test

VASCEPA significantly reduced TG, non-HDL-C, Apo B, VLDL-C, TC and HDL-C levels from baseline relative to placebo. The reduction in TG observed with VASCEPA was not associated with elevations in LDL-C relative to placebo.

The effect of VASCEPA on cardiovascular mortality and morbidity in patients with mixed dyslipidemia has not been determined.